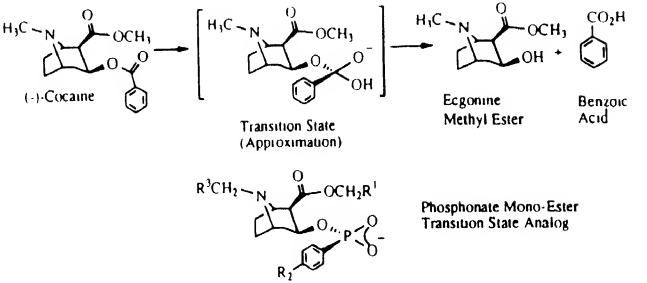
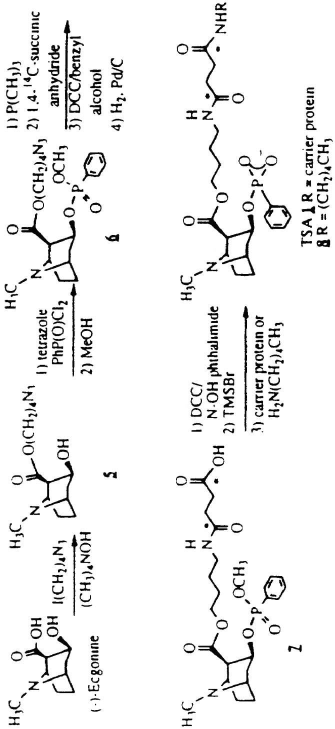
T08280' 4270h660

FIG. 1



TSA 1 $R^1 = (CH_2)_3NH^{14}CO(CH_2)_2{}^{14}CONH$–carrier protein; $R^2 = R^3 = H$
TSA 2 $R^2 = (CH_2)_3NH^{14}CO(CH_2)_2{}^{14}CONH$–carrier protein; $R^1 = R^3 = H$
TSA 3 $R^3 = (CH_2)_2NH^{14}CO(CH_2)_2{}^{14}CONH$–carrier protein; $R^2 = R^1 = H$
Free TSA 4 $R^1 = R^2 = R^3 = H$

FIG. 2


(-)-Ecgonine
I(CH2)4N3
(CH3)4NOH
5
1) tetrazole
PhP(O)Cl2
2) MeOH
6
1) P(CH3)3
2) 1,4-14C-succinic anhydride
3) DCC/benzyl alcohol
4) H2, Pd/C
7
1) DCC/
N-OH phthalimide
2) TMSBr
3) carrier protein or
H2N(CH2)4CH3
TSA 1 R = carrier protein
8 R = (CH2)4CH3

099/07227 .082801

FIG. 3

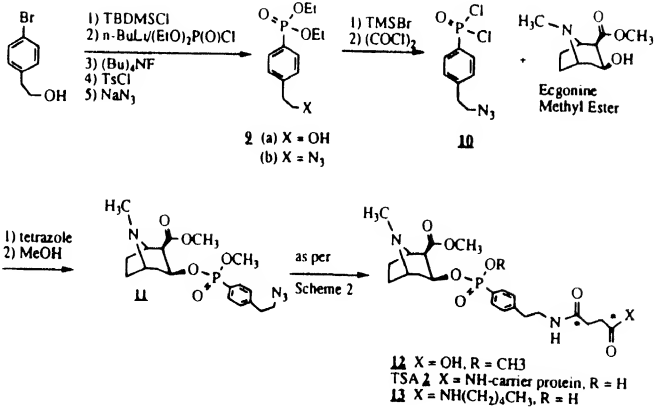


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FIG. 4

Scheme 4

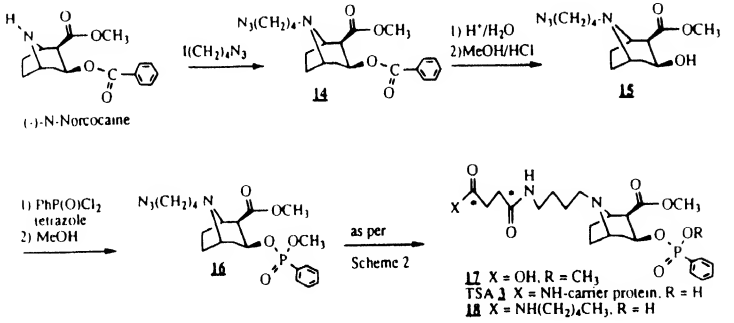

FIG. 5

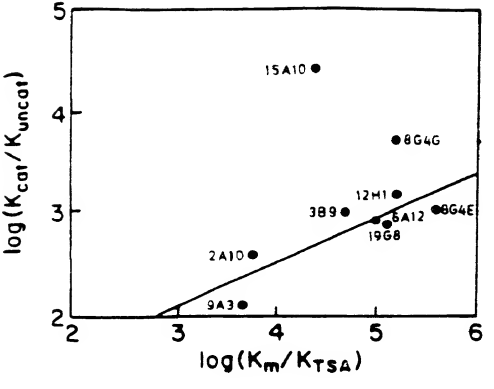
15A10
8G4G
12H1
3B9
6A12
8G4E
19G8
2A10
9A3
log(Kcat/Kuncat)
log(Km/KTSA)
2
3
4
5
6

FIG. 6

LAMBDA LIGHT CHAIN ALIGNMENT

```
9A(lam9) vari     1:----------TWPGETVTLTCRSSTGTITTSNYANWVQEKPDHLFSGLIGINNNRPPGVP
19G(lam5) vari    1:----------.R..........A.......................V.........
15A10L Vari       1:AVVTQESALT.S.................SD.................V..Y......
G7(lam4) vari     1:----------.RA..........S....AN..GS.........T....VS...G....
                             *  ********** **** **  ********** ****  * * ****

9A(lam9) vari    61:ARFSGSLIGDKAVLTITGAQTEDEAIYFCALWYSNHWVFGGGTKLTVLG
19G(lam5) vari   61:..........T.A.....................................
15A10 Vari       61:.......T.....................................
G7(lam4) vari    61:.................G.............N...F............
                    ******* ** * ***** ************ *** ************
```

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FIG. 7

KAPPA LIGHT CHAIN ALIGNMENT

```
3B9 K vari      1:DIVMTQDELSNPVTSGESVSISCRSSRSLLYRDGKTYLNWFLQRPGRSPQLLIYLMSTRS
6A12 k vari     1:..M.....................................................A
12H(L2) k vari  1:..M.....................................................A
2A k vari       1:...I.....................K....E.............Q..H.........A
E2(L7) k Vari   1:EL....SP.TLS..I.QPA....K..Q....S.........F....Q..KR....V.KLD
                   * **  *   ** *  **** ** **** ********** **** **  **** *

3B9 K vari      61:SGVSDRFSGSGSGTDFTLEISRVKAEDVGVYYC-QHFVDYPFTFGSGTKLEIKR
6A12 k vari     61:.................................-...E.....................
12H(L2) k vari  61:.................................-.....................
2A k vari       61:.............................A....-.Q..E.............R.
E2(L7) k Vari   61:...P...T.....K....K....E...L.L...V.GY-TF.L...A.....L..
                   *** *** ***** **** **** *** * *** *      * *** *****  *
```

FIG. 8

HEAVY CHAIN ALIGNMENT

```
3B9 vari      1:DVQLQESGPGLVKPSQSLSLTCTVTGNSITSDYAWTWIRQFPGNKLEWMGYIR-HIYGTR
6A12 heavy    1:.....................................................-......
12H H vari    1:.......................................K........L....-......
2AH-3 vari    1:---------E................Y........N........R........-YSGI..
9(H-3) vari   1:------...E....GA.VK.S.KAS.YPF.-..NMY.VK.SH.KS...I...DPSNG.IF
19h6-3 vari   1:EIH..Q...E....GA.VK.S.KAS.Y.F.-..NMY.VK.SH.KS...I...DP.NG.IF
15A10 vari    1:E........E....GA.VKVS.KAS.Y.F.-..NMY.VK.NH.ES...IA..DPSNGD.F
E2(H8) vari   1:VQL.E-..AE..M.GA.VKMS.KAS.YTF.-.HWMH.VK.R..QG...I.T.DLSDTY.G
G7(H8) Vari   1:VQL.E-..AE....GA.VE.S.RTS.YTF.-T.YIY.VK.R..QG...I.GMNPGNGV.Y
                            ** *  *    *   *   *      *     *  ***

3B9 vari     61:YNPSLISRISITRDTSKNQFFLQLDSVTAEDTATYYCVRYHYYGSAYWGQGTLVTVSA
6A12 heavy   61:..........................................................
12H H vari   61:..........................................................
2AH-3 vari   61:.....K............K.....N...T..........I....YGN.....TL.GLP
9(H-3) vari  61:..QKFKG.ATL.V.K.S.TA.MH.N.L.S..S.V...A.GGGL-F............E
19H6-3 vari  61:..QKFKG.ATL.V.K.S.TA.MH.N.L.S..S.V...A.GGGL-F....R........
15A10 vari   61:..QKFQGKATV.L.K.SSTA.MH.N.L.S..S.V...A.GGGL-F.F...........
E2(H8) vari  61:..QNFKG.ATL.L.E.S.TAYM..S.L.S..S.V...S.RG---FD......TL...S
G7(H8) Vari  61:F.EKFKN.ATL.V.R.SSIAYM..S.L.S..S.V...T.VGNL-F....R........
                 *         * * *       * * * ** * *** *        ** **  *
```

FIG. 9

```
         10         20         30         40         50         60
GCTGTTGTTACTCAGGAGTCTGCTCTAACTACATCACCTGGTGAAACAGTCACACTCACT
A  V  V  T  Q  E  S  A  L  T  T  S  P  G  E  T  V  T  L  T

         70         80         90        100        110        120
TGTCGCTCAAGTACTGGGACTATTACAAGTGATAACTATGCCAACTGGGTCCAAGAAAAA
C  R  S  S  T  G  T  I  T  S  D  N  Y  A  N  W  V  Q  E  K

        130        140        150        160        170        180
CCAGATCATTTATTCAGTGGTCTAATAGGTGTTAATAATTACCGACCTCCAGGTGTTCCT
P  D  H  L  F  S  G  L  I  G  V  N  N  Y  R  P  P  G  V  P

        190        200        210        220        230        240
GCCAGATTCTCAGGCTCCCTGACTGGAGACAAGGCTGTCCTCACCATCACAGGGGCACAG
A  R  F  S  G  S  L  T  G  D  K  A  V  L  T  I  T  G  A  Q

        250        260        270        280        290        300
ACTGAGGATGAGGCAATATATTTCTGTGCTCTATGGTACAGCAACCACTGGGTGTTCGGT
T  E  D  E  A  I  Y  F  C  A  L  W  Y  S  N  H  W  V  F  G

        310        320        330        340        350        360
GGAGGAACCAAACTGACTGTCCTAGGCCAGCCCAAGTCTTCGCCATCAGTCACCCTGTTT
G  G  T  K  L  T  V  L  G
```

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FIG. 10

```
        10         20         30         40         50         60
TCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGGTATCCTGTAAGGCTTCTGGT
S  G  P  E  L  V  K  P  G  A  S  V  K  V  S  C  K  A  S  G

        70         80         90        100        110        120
TATTCATTCACTGACTACAATATGTACTGGGTGAAGCAGAACCATGGAGAGAGCCTTGAA
Y  S  F  T  D  Y  N  M  Y  W  V  K  Q  N  H  G  E  S  L  E

       130        140        150        160        170        180
TGGATTGCATATATTGATCCTTCCAATGGTGATACTTTCTACAACCAGAAATTCCAGGGC
W  I  A  Y  I  D  P  S  N  G  D  T  F  Y  N  Q  K  F  Q  G

       190        200        210        220        230        240
AAGGCCACAGTGACTCTTGACAAGTCCTCCAGTACAGCCTTCATGCATCTCAACAGCCTG
K  A  T  V  T  L  D  K  S  S  S  T  A  F  M  H  L  N  S  L

       250        260        270        280        290        300
ACATCTGAGGACTCTGCAGTCTATTACTGTGCAAGAGGGGGGGGCCTGTTTGCTTTCTGG
T  S  E  D  S  A  V  Y  Y  C  A  R  G  G  G  L  F  A  F  W

       310        320        330
GGGCAAGGGACTCTGGTCACTGTCTCTGCA
G  Q  G  T  L  V  T  V  S  A
```

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FIG. 11

```
        10         20         30         40         50         60
GTCGCATGCTCCCGGNCGNCATGGNCGCGGGATTGGGAATTCCACGAGGCCGGGGGAGAC
                                              T  R  P  G  E  T

        70         80         90        100        110        120
AGTCACACTCACTTGTCGTTCAAGTGCTGGGACTATTACAACTAGTAACTATGCCAACTG
 V  T  L  T  C  R  S  S  A  G  T  I  T  T  S  N  Y  A  N  W

       130        140        150        160        170        180
GGTCCAAGAAAAACCAGATCATTTATTCAGTGGTCTAATAGGTGTTAACAACAACCGACC
 V  Q  E  K  P  D  H  L  F  S  G  L  I  G  V  N  N  N  R  P

       190        200        210        220        230        240
TCCAGGTGTTCCTGCCAGATTCTCAGGCTCCCTGATTGGAGACACGGCTGCCCTCACCAT
 P  G  V  P  A  R  F  S  G  S  L  I  G  D  T  A  A  L  T  I

       250        260        270        280        290        300
CACAGGGGCACAGACTGAGGATGAGGCAATATATTTCTGTGCTCTATGGTACAGCAACCA
 T  G  A  Q  T  E  D  E  A  I  Y  F  C  A  L  W  Y  S  N  H

       310        320        330        340        350        360
CTGGGTGTTCGGTGGAGGAACCAAACTGACTGTCCTAGGCCAGCCCAAGTCTTCGNCATC
 W  V  F  G  G  G  T  K  L  T  V  L  G
```

SUBSTITUTE SHEET (RULE 26)

FIG. 12

```
        10         20         30         40         50         60
GAATTCGGCACGAGCAGGAACTACAGGTGTCCACTCTGAGATCCACCTGCAGCAGTCTGG
                                       E  I  H  L  Q  Q  S  G

        70         80         90        100        110        120
ACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGTTATCCTGCAAGGCTTCTGGTTACTC
 P  E  L  V  K  P  G  A  S  V  K  L  S  C  K  A  S  G  Y  S

       130        140        150        160        170        180
ATTCACTGACTACAACATGTACTGGGTGAAACAGAGCCATGGAAAGAGCCTTGAGTGGAT
 F  T  D  Y  N  M  Y  W  V  K  Q  S  H  G  K  S  L  E  W  I

       190        200        210        220        230        240
TGGATATATTGATCCTCACAATGGTGGTATTTTCTACAACCAGAAGTTCAAGGGCAGGGC
 G  Y  I  D  P  H  N  G  G  I  F  Y  N  Q  K  F  K  G  R  A

       250        260        270        280        290        300
CACATTGACTGTTGACAAGTCCTCCAACACAGCCTTCATGCATCTCAACAGCCTGACATC
 T  L  T  V  D  K  S  S  N  T  A  F  M  H  L  N  S  L  T  S

       310        320        330        340        350        360
TGAGGACTCTGCAGTCTATTACTGTGCAAGAGGGGGGGGCCTGTTTGCTTACTGGGGCCG
 E  D  S  A  V  Y  Y  C  A  R  G  G  G  L  F  A  Y  W  G  R

       370        380        390        400        410        420
AGGGACTCTGGTCACTGTCTCTGCAGCCAAAACGACACCCCCATCTGTCTATCCACTGGC
 G  T  L  V  T  V  S  A
```

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FIG. 13

```
              10        20        30        40        50        60
GTCGCATGCTCCCGGNCGCCATGGNCGCGGGATTGGGAATTCCACGTGGCCGGGGGAGAC
                                              T  W  P  G  E  T

              70        80        90       100       110       120
AGTCACACTCACTTGTCGCTCAAGTACTGGGACTATTACAACTAGTAACTATGCCAACTG
 V  T  L  T  C  R  S  S  T  G  T  I  T  T  S  N  Y  A  N  W

             130       140       150       160       170       180
GGTCCAAGAAAAACCAGATCATTTATTCAGTGGTCTGATAGGTATTAACAACAACCGACC
 V  Q  E  K  P  D  H  L  F  S  G  L  I  G  I  N  N  N  R  P

             190       200       210       220       230       240
TCCAGGTGTTCCTGCCAGATTCTCAGGCTCCCTGATTGGAGACAAGGCTGTCCTCACCAT
 P  G  V  P  A  R  F  S  G  S  L  I  G  D  K  A  V  L  T  I

             250       260       270       280       290       300
CACAGGGGCACAGACTGAGGATGAGGCAATATATTTCTGTGCTCTATGGTACAGCAACCA
 T  G  A  Q  T  E  D  E  A  I  Y  F  C  A  L  W  Y  S  N  H

             310       320       330       340       350       360
CTGGGTGTTCGGTGGAGGAACCAAACTGACTGTCCTAGGCCAGCCCAAGTCTTCGNCATC
 W  V  F  G  G  G  T  K  L  T  V  L  G
```

FIG. 14

```
        70         80         90        100        110        120
GGTCCAGCTGCTCGAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGTTATC
                  S  G  P  E  L  V  K  P  G  A  S  V  K  L  S

       130        140        150        160        170        180
CTGCAAGGCTTCTGGTTACCCATTCACTGACTACAACATGTACTGGGTGAAGCAGAGCCA
 C  K  A  S  G  Y  P  F  T  D  Y  N  M  Y  W  V  K  Q  S  H

       190        200        210        220        230        240
TGGAAAGAGCCTTGAGTGGATTGGATATATTGATCCTTCCAATGGTGGTATTTTTTACAA
 G  K  S  L  E  W  I  G  Y  I  D  P  S  N  G  G  I  F  Y  N

       250        260        270        280        290        300
CCAGAAGTTCAAGGGCAGGGCCACATTGACTGTTGACAAGTCCTCCAACACAGCCTTCAT
 Q  K  F  K  G  R  A  T  L  T  V  D  K  S  S  N  T  A  F  M

       310        320        330        340        350        360
GCATCTCAACAGCCTGACATCTGAGGACTCTGCAGTCTATTACTGTGCAAGAGGGGGGGG
 H  L  N  S  L  T  S  E  D  S  A  V  Y  Y  C  A  R  G  G  G

       370        380        390        400        410        420
CCTGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGAAGCCAAAACGAAACC
 L  F  A  Y  W  G  Q  G  T  L  V  T  V  S  E
```

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FIG. 15

```
         70         80         90        100        110        120
AGGCGGCCGCACTAGTGATTGGGAATTCCACGAGGGCGGGGGAGACAGTCACACTCACTT
                                T  R  A  G  E  T  V  T  L  T  C

        130        140        150        160        170        180
GTCGCTCAAGTAGTGGGACTATTACAGCTAATAACTATGGCAGCTGGGTCCAGGAAAAGC
  R  S  S  S  G  T  I  T  A  N  N  Y  G  S  W  V  Q  E  K  P

        190        200        210        220        230        240
CAGATCATTTATTCACTGGTCTAATAGGTGTTAGCAACAACCGAGGTCCAGGTGTTCCTG
  D  H  L  F  T  G  L  I  G  V  S  N  N  R  G  P  G  V  P  A

        250        260        270        280        290        300
CCAGATTCTCAGGCTCCCTAATTGGAGACAAGGCTGTCCTCACCATCACGGGGGGGCAGA
  R  F  S  G  S  L  I  G  D  K  A  V  L  T  I  T  G  G  Q  T

        310        320        330        340        350        360
CTGAGGATGAGGCAATTTATTTCTGTGCTCTATGGAACAGCAACCATTTCGTGTTCGGTG
  E  D  E  A  I  Y  F  C  A  L  W  N  S  N  H  F  V  F  G  G

        370        380        390        400        410        420
GAGGAACCAAACTGACTGTCCTAGGGCAGACCAAGTCTTTCGGCATCAAGCACCCTGTTT
  G  T  K  L  T  V  L  G  Q
```

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FIG. 16

```
        10         20         30         40         50         60
CCATTGGGCCCGACGTCGCATGCTCCCGGCCGCCATGGCCGCGGGATTAGGTCCAACTTC
                                                  V  Q  L  L

        70         80         90        100        110        120
TCGAGTCTGGGGCTGAACTGGTGAAGCCTGGGGCTTCAGTGGAGTTGTCCTGCAGGACTT
  E  S  G  A  E  L  V  K  P  G  A  S  V  E  L  S  C  R  T  S

       130        140        150        160        170        180
CTGGCTACACCTTCACCACCTACTATATTTACTGGGTAAAACAGAGGCCTGGACAAGGCC
  G  Y  T  F  T  T  Y  Y  I  Y  W  V  K  Q  R  P  G  Q  G  L

       190        200        210        220        230        240
TTGAGTGGATTGGGGGGATGAATCCTGGCAATGGTGTTACTTACTTCAATGAAAAATTCA
  E  W  I  G  G  M  N  P  G  N  G  V  T  Y  F  N  E  K  F  K

       250        260        270        280        290        300
AGAACAGGGCCACACTGACTGTGGACAGATCCTCCAGCATTGCCTACATGCAACTCAGCA
  N  R  A  T  L  T  V  D  R  S  S  S  I  A  Y  M  Q  L  S  S

       310        320        330        340        350        360
GCCTGACATCTGAGGACTCTGCGGTCTATTACTGTACACGGGTGGGTAACCTCTTTGCTT
  L  T  S  E  D  S  A  V  Y  Y  C  T  R  V  G  N  L  F  A  Y

       370        380        390        400        410        420
ACTGGGGCCGAGGGACTCTGGTCACTGTCTCTGCAGCCAAAACGACACCCCACTTTCTAT
  W  G  R  G  T  L  V  T  V  S  A
```

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FIG. 17

```
        10         20         30         40         50         60
GATATTGTGATGACCCAGGATGAACTCTCCAATCCTGTCACTTCTGGAGAATCAGTTTCC
D  I  V  M  T  Q  D  E  L  S  N  P  V  T  S  G  E  S  V  S

        70         80         90        100        110        120
ATCTCCTGCAGGTCTAGTAGGAGTCTCCTATATAGGGATGGGAAGACATACTTGAATTGG
I  S  C  R  S  S  R  S  L  L  Y  R  D  G  K  T  Y  L  N  W

       130        140        150        160        170        180
TTTCTGCAGAGACCAGGACGATCTCCTCAACTCCTGATCTATTTGATGTCCACCCGTTCA
F  L  Q  R  P  G  R  S  P  Q  L  L  I  Y  L  M  S  T  R  S

       190        200        210        220        230        240
TCAGGAGTCTCAGACCGGTTTAGTGGCAGTGGGTCAGGAACAGATTTCACCCTGGAAATC
S  G  V  S  D  R  F  S  G  S  G  S  G  T  D  F  T  L  E  I

       250        260        270        280        290        300
AGTAGAGTGAAGGCTGAGGATGTGGGTGTGTATTACTGTCAACACTTTGTAGACTATCCA
S  R  V  K  A  E  D  V  G  V  Y  Y  C  Q  H  F  V  D  Y  P

       310        320        330
TTCACGTTCGGCTCGGGGACAAAGTTGGAGATAAAACGG
F  T  F  G  S  G  T  K  L  E  I  K  R
```

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FIG. 18

```
         10         20         30         40         50         60
GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCCTC
D  V  Q  L  Q  E  S  G  P  G  L  V  K  P  S  Q  S  L  S  L

         70         80         90        100        110        120
ACCTGGCACTGTCACTGGCAATTCAATCACCAGTGATTATGCCTGGACCTGGATCCGGCAG
T  C  T  V  T  G  N  S  I  T  S  D  Y  A  W  T  W  I  R  Q

        130        140        150        160        170        180
TTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGGCACATTTATGGCACTAGGTAC
F  P  G  N  K  L  E  W  M  G  Y  I  R  H  I  Y  G  T  R  Y

        190        200        210        220        230        240
AACCCTTCTCTCATAAGTCGAATCTCTATCACTCGAGACACGTCCAAGAACCAGTTCTTC
N  P  S  L  I  S  R  I  S  I  T  R  D  T  S  K  N  Q  F  F

        250        260        270        280        290        300
CTGCAGTTGGATTCTGTGACTGCTGAGGACACAGCCACATATTATTGTGTAAGATATCAT
L  Q  L  D  S  V  T  A  E  D  T  A  T  Y  Y  C  V  R  Y  H

        310        320        330        340        350        360
TACTACGGTTCGGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCAGCCAAAACG
Y  Y  G  S  A  Y  W  G  Q  G  T  L  V  T  V  S  A  A  K  T

ACACCC
T  P
```

FIG. 19

```
        10         20         30         40         50         60
GATATGGTGATGACGCAAGATGAACTCTCCAATCCTGTCACTTCTGGAGAATCAGTTTCC
D  M  V  M  T  Q  D  E  L  S  N  P  V  T  S  G  E  S  V  S

        70         80         90        100        110        120
ATCTCCTGCAGGTCTAGTAGGAGTCTCCTATATAGGGATGGGAAGACATACTTGAATTGG
I  S  C  R  S  S  R  S  L  L  Y  R  D  G  K  T  Y  L  N  W

       130        140        150        160        170        180
TTTCTGCAGAGACCAGGACGATCTCCTCAACTCCTGATCTATTTGATGTCCACCCGTGCA
F  L  Q  R  P  G  R  S  P  Q  L  L  I  Y  L  M  S  T  R  A

       190        200        210        220        230        240
TCAGGAGTCTCAGACCGGTTTAGTGGCAGTGGGTCAGGAACAGATTTCACCCTGGAAATC
S  G  V  S  D  R  F  S  G  S  G  S  G  T  D  F  T  L  E  I

       250        260        270        280        290        300
AGTAGAGTGAAGGCTGAGGATGTGGGTGTGTATTACTTTCAACACTTTGAAGACTATCCA
S  R  V  K  A  E  D  V  G  V  Y  Y  F  Q  H  F  E  D  Y  P

       310        320        330        340        350        360
TTCACGTTCGGCTCGGGGACAAAATTGGAGATAAAACGGGCTGATGCTGCACCAACTGTA
F  T  F  G  S  G  T  K  L  E  I  K  R

TCCATCTT
```

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FIG. 20

```
        10         20         30         40         50         60
GACGTGCAGTTGCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCCTC
D  V  Q  L  Q  E  S  G  P  G  L  V  K  P  S  Q  S  L  S  L

        70         80         90        100        110        120
ACCTGCACTGTCACTGGCAATTCAATCACCAGTGATTATGCCTGGACCTGGATCCGGCAG
T  C  T  V  T  G  N  S  I  T  S  D  Y  A  W  T  W  I  R  Q

       130        140        150        160        170        180
TTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGGCACATTTATGGCACTAGGTAC
F  P  G  N  K  L  E  W  M  G  Y  I  R  H  I  Y  G  T  R  Y

       190        200        210        220        230        240
AACCCTTCTCTCATAAGTCGAATCTCTATCACTCGAGACACGTCCAAGAACCAGTTCTTC
N  P  S  L  I  S  R  I  S  I  T  R  D  T  S  K  N  Q  F  F

       250        260        270        280        290        300
CTGCAGTTGGATTCTGTGACTGCTGAGGACACAGCCACATATTATTGTGTAAGATATCAT
L  Q  L  D  S  V  T  A  E  D  T  A  T  Y  Y  C  V  R  Y  H

       310        320        330        340        350        360
TACTACGGTTCGGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCAGCCAAAACG
Y  Y  G  S  A  Y  W  G  Q  G  T  L  V  T  V  S  A  A  K  T

ACACCC
T  P
```

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FIG. 21

```
        10         20         30         40         50         60
GATATGGTGATGACGCAAGACGAACTCTCCAATCCTGTCACTTCTGGAGAATCAGTTTCC
D  M  V  M  T  Q  D  E  L  S  N  P  V  T  S  G  E  S  V  S

        70         80         90        100        110        120
ATCTCCTGCAGGTCTAGTAAGAGTCTCCTATATGAGGATGGGAAGACATACTTGAATTGG
I  S  C  R  S  S  K  S  L  L  Y  E  D  G  K  T  Y  L  N  W

       130        140        150        160        170        180
TTTCTGCAGAGACCAGGACAATCTCCTCACCTCCTGATCTATTTGATGTCCACCCGTGCA
F  L  Q  R  P  G  Q  S  P  H  L  L  I  Y  L  M  S  T  R  A

       190        200        210        220        230        240
TCAGGAGTCTCAGACCGGTTTAGTGGCAGTGGGTCAGGAACAGATTTCACCCTGGAAATC
S  G  V  S  D  R  F  S  G  S  G  S  G  T  D  F  T  L  E  I

       250        260        270        280        290        300
AGTAGAGTGAAGGCTGAGGATGTGGGTGCGTATTACTGTCAACAATTTGTAGAGTATCCA
S  R  V  K  A  E  D  V  G  A  Y  Y  C  Q  Q  F  V  E  Y  P

       310        320        330        340        350        360
TTCACGTTCGGCTCGGGGACAAAGTTGGAAATAAGACGGGTTGATGCCGCACCAACTGTA
F  T  F  G  S  G  T  K  L  E  I  R  R

TCCATCTT
```

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FIG. 22

```
        10         20         30         40         50         60
CATTGGGCCCACGTCGAATGNTCCCGGNCGNCATGGNCGNGGGATTGANAGGGGGNCGGA
                                                              E

        70         80         90        100        110        120
GCTGGTGAAGCCTTCTCAGTCTCTGTCCCTCACCTGCACTGTCACTGGCTACTCAATCAC
 L  V  K  P  S  Q  S  L  S  L  T  C  T  V  T  G  Y  S  I  T

       130        140        150        160        170        180
CAGTGATTATGCCTGGAACTGGATCCGGCAGTTTCCAGGAAACAGACTGGAGTGGATGGG
 S  D  Y  A  W  N  W  I  R  Q  F  P  G  N  R  L  E  W  M  G

       190        200        210        220        230        240
CTACATAAGGTACAGTGGTATCACTAGGTACAACCCATCTCTCAAAAGTCGAATCTCTAT
 Y  I  R  Y  S  G  I  T  R  Y  N  P  S  L  K  S  R  I  S  I

       250        260        270        280        290        300
CACTCGAGACACATCCAAGAACAAGTTCTTCCTGCAGTTAAATTCTGTGACTACTGAGGA
 T  R  D  T  S  K  N  K  F  F  L  Q  L  N  S  V  T  T  E  D

       310        320        330        340        350        360
CACAGCCACTTATTACTGTGTAAGAATTCATTACTACGGCTACGGCAACTGGGGGCAAGG
 T  A  T  Y  Y  C  V  R  I  H  Y  Y  G  Y  G  N  W  G  Q  G

       370        380        390        400        410        420
CACCACTCTCACAGGTCTTCCTCAAGAGTCTGGGAAGAAATCCCACCCATCTTCCCCACT
 T  T  L  T  G  L  P
```

FIG. 23

```
        10         20         30         40         50         60
NCCTTGGGCCGANGGCGCATGCTCCCGGCCGCCATGGCCGCGGGATTAGAGCGATATGGT
                                                    D  M  V

        70         80         90        100        110        120
GATGACGCAGGATGAACTCTCCAATCCTGTCACTTCTGGAGAATCAGTTTCCATCTCCTG
 M  T  Q  D  E  L  S  N  P  V  T  S  G  E  S  V  S  I  S  C

       130        140        150        160        170        180
CAGGTCTAGTAGGAGTCTCCTATATAGGGATGGGAAGACATACTTGAATTGGTTTCTGCA
 R  S  S  R  S  L  L  Y  R  D  G  K  T  Y  L  N  W  F  L  Q

       190        200        210        220        230        240
GAGACCAGGACGATCTCCTCAACTCCTGATCTATTTGATGTCCACCCGTGCATCAGGAGT
 R  P  G  R  S  P  Q  L  L  I  Y  L  M  S  T  R  A  S  G  V

       250        260        270        280        290        300
CTCAGACCGGTTTAGTGGCAGTGGGTCAGGAACAGATTTCACCCTGGAAATCAGTAGAGT
 S  D  R  F  S  G  S  G  S  G  T  D  F  T  L  E  I  S  R  V

       310        320        330        340        350        360
GAAGGCTGAGGATGTGGGTGTGTATTACTGTCAACACTTTGTAGACTATCCATTCACGTT
 K  A  E  D  V  G  V  Y  Y  C  Q  H  F  V  D  Y  P  F  T  F

       370        380        390        400        410        420
CGGCTCGGGGACAAAGTTGGAGATAAAACGGGTTGATGCTGNANCAACTGTATCCATCTT
 G  S  G  T  K  L  E  I  K  R
```

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FIG. 24

```
        70         80         90        100        110        120
CTAGTGATTGCTCTAGAGCGACGTGCAGTTGCAGGAGTCGGGACCTGGACTGGTGAAACC
                    D  V  Q  L  Q  E  S  G  P  G  L  V  K  P

       130        140        150        160        170        180
TTCTCAGTCTCTGTCCCTCACCTGCACTGTCACTGGTAATTCAATCACCAGTGATTATGC
 S  Q  S  L  S  L  T  C  T  V  T  G  N  S  I  T  S  D  Y  A

       190        200        210        220        230        240
CTGGACCTGGATCCGGAAGTTTCCAGGAAACAAACTGGAGTGGTTGGGCTACATAAGGCA
 W  T  W  I  R  K  F  P  G  N  K  L  E  W  L  G  Y  I  R  H

       250        260        270        280        290        300
CATTTATGGCACTAGGTACAACCCTTCTCTCATAAGTCGAATCTCTATCACTCGAGACAC
 I  Y  G  T  R  Y  N  P  S  L  I  S  R  I  S  I  T  R  D  T

       310        320        330        340        350        360
GTCCAAGAACCAGTTCTTCCTGCAGTTGGATTCTGTGACTGCTGAGGACACAGCCACATA
 S  K  N  Q  F  F  L  Q  L  D  S  V  T  A  E  D  T  A  T  Y

       370        380        390        400        410        420
TTATTGTGTAAGATATCATTACTACGGGTCGGCTTACTGGGGGCAAGGGACTCTGGTCAC
 Y  C  V  R  Y  H  Y  Y  G  S  A  Y  W  G  Q  G  T  L  V  T

       430        440        450        460        470        480
TGTCTCTGCAGGCAAAACGANACCCCATCTGTCTATCCACTGGCCCCGGAACGCCGCCAG
 V  S  A
```

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FIG. 25

```
        10         20         30         40         50         60
TTNAAGGCCCNGACGCCGCATAGCTCNCGGCCGCCATGGCCGNGGGATTCCAGTTCCGAG
                                                              E

        70         80         90        100        110        120
CTCGTGATGACACAGTCTCCACTCACTTTGTCGGTAACCATTGGACAACCAGCCTCTATC
L  V  M  T  Q  S  P  L  T  L  S  V  T  I  G  Q  P  A  S  I

       130        140        150        160        170        180
TCTTGCAAGTCAAGTCAGAGCCTCTTATATAGTGATGGAAAAACCTATTTGAATTGGTTC
S  C  K  S  S  Q  S  L  L  Y  S  D  G  K  T  Y  L  N  W  F

       190        200        210        220        230        240
TTCCAGAGGCCAGGCCAGTCTCCAAAGCGCCTAATCTATCTGGTGTCTAAACTGGACTCT
F  Q  R  P  G  Q  S  P  K  R  L  I  Y  L  V  S  K  L  D  S

       250        260        270        280        290        300
GGAGTCCCTGACAGGTTCACTGGCAGTGGATCAGGAAAAGATTTTACACTGAAAATCAGC
G  V  P  D  R  F  T  G  S  G  S  G  K  D  F  T  L  K  I  S

       310        320        330        340        350        360
AGAGTGGAGGCTGAGGATTTGGGACTTTATTACTGCGTTCAAGGGTACACATTTCCGCTC
R  V  E  A  E  D  L  G  L  Y  Y  C  V  Q  G  Y  T  F  P  L

       370        380        390        400        410        420
ACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAACGGGTGATGCTGACCAACTTGTTTCAT
T  F  G  A  G  T  K  L  E  L  K  R
```

SUBSTITUTE SHEET (RULE 26)

FIG. 26

```
        10         20         30         40         50         60
TTGGGCCCGGACGTCGCATGCTCCCGGCCGCCATGGNCGNGGGATTAGGTCCAACTTCTC
                                                   V  Q  L  L

        70         80         90        100        110        120
GAGTCTGGGGCTGAGCTTGTGATGCCTGGGGCTTCAGTGAAGATGTCCTGCAAGGCTTCT
E  S  G  A  E  L  V  M  P  G  A  S  V  K  M  S  C  K  A  S

       130        140        150        160        170        180
GGCTACACATTCACTGACCACTGGATGCACTGGGTGAAGCAGAGGCCTGGACAAGGCCTT
G  Y  T  F  T  D  H  W  M  H  W  V  K  Q  R  P  G  Q  G  L

       190        200        210        220        230        240
GAGTGGATCGGAACGATTGATCTTTCTGATACTTATACTGGCTACAATCAAAACTTCAAG
E  W  I  G  T  I  D  L  S  D  T  Y  T  G  Y  N  Q  N  F  K

       250        260        270        280        290        300
GGCAGGGCCACATTGACTCTCGACGAATCCTCCAACACAGCCTACATGCAGCTCAGCAGC
G  R  A  T  L  T  L  D  E  S  S  N  T  A  Y  M  Q  L  S  S

       310        320        330        340        350        360
CTGACATCTGAGGACTCTGCGGTCTATTACTGTTCAAGAAGGGGCTTTGACTACTGGGGG
L  T  S  E  D  S  A  V  Y  Y  C  S  R  R  G  F  D  Y  W  G

       370        380        390        400        410        420
CAAGGCACCACTCTCACAGTCTCCTCAGGCAAAACGACAACCCCATCTTGTCTNTCCACT
Q  G  T  T  L  T  V  S  S
```

SUBSTITUTE SHEET (RULE 26)

FIG. 27

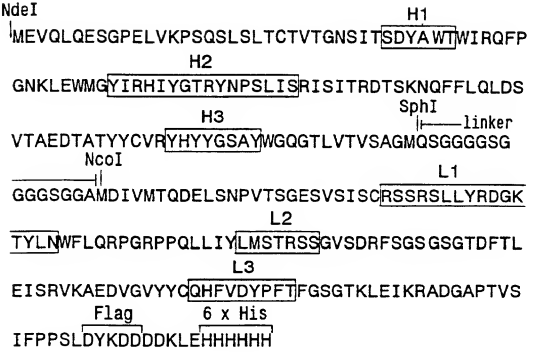
NdeI
H1
MEVQLQESGPELVKPSQSLSLTCTVTGNSITSDYAWTWIRQFP
H2
GNKLEWMGYIRHIYGTRYNPSLISRISITRDTSKNQFFLQLDS
SphI
H3
linker
VTAEDTATYYCVRYHYYGSAYWGQGTLVTVSAGMQSGGGGSG
NcoI
L1
GGGSGGAMDIVMTQDELSNPVTSGESVSISCRSSRSLLYRDGK
L2
TYLNWFLQRPGRPPQLLIYLMSTRSSGVSDRFSGSGSGTDFTL
L3
EISRVKAEDVGVYYCQHFVDYPFTFGSGTKLEIKRADGAPTVS
Flag
6 x His
IFPPSLDYKDDDDKLEHHHHHH

FIG. 28A

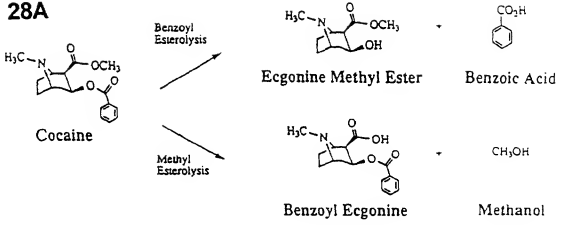

FIG. 28B

Transition State
Benzoyl Esterolysis
(Approximation)

Transition-State Analog
Free TSA R=H
TSA-I R=$(CH_2)_3NHCO(CH_2)_2CONH$-BSA

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FIG. 29

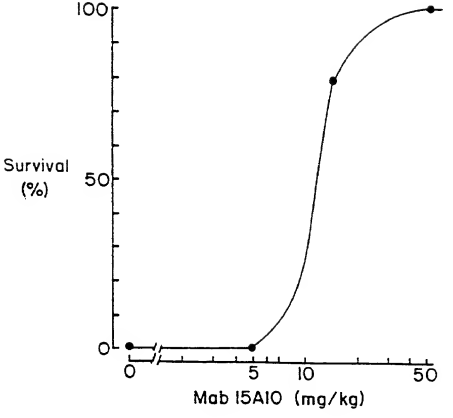

FIG. 30A

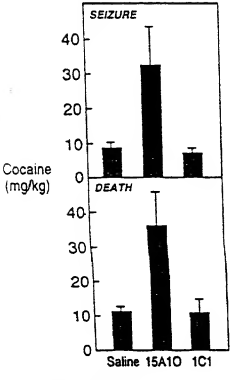

FIG. 30B

FIG. 30C

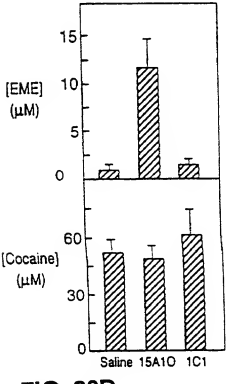

FIG. 30D